

AMENDMENTS TO THE SPECIFICATION:

Please amend the specification as indicated below.

Page 1, second full paragraph:

The present invention relates to the use of an inhibitor of the renin-angiotensin system or a pharmaceutically acceptable derivative thereof, optionally together with another ~~an-
other~~ antihypertensive, a cholesterol lowering agent, a diuretic or aspirin, in the manufacture of a medicament for the prevention of cardiovascular events; to a method of preventing cardiovascular events comprising administering to a patient in need of such prevention an effective amount of an inhibitor of the renin angiotensin system or a pharmaceutically acceptable derivative thereof, optionally together with another ~~an-
other~~ antihypertensive, a cholesterol lowering agent, a diuretic or aspirin; or to a combination product containing an ~~[[an]]~~ inhibitor of the renin-angiotensin system or a pharmaceutically acceptable derivative thereof and a cholesterol lowering agent.

Page 2, fourth full paragraph:

The present invention ~~inventions~~ further relates to the use of an inhibitor of the renin-angiotensin system or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for the prevention of myocardial infarction (MI), worsening of angina₁ and cardiac arrest.

Page 2, fifth full paragraph:

Furthermore, the present invention relates to the use of an inhibitor of the renin-angiotensin system or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for the prevention of cardiovascular events such as₁ for example₁ myocardial infarction (MI), worsening of angina or cardiac arrest in a patient with an increased cardiovascular risk, for example₁ due to a manifest coronary ~~coronary~~

heart disease, a history of transient ischaemic attacks or stroke, or a history of peripheral vascular disease.

Page 3, first full paragraph:

More generally, the present invention relates to the use of an inhibitor of the renin-angiotensin system or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for the prevention of cardiovascular events in patients with no evidence of left ventricular dysfunction or heart failure.

Page 3, second full paragraph:

The present invention further relates to the use of an inhibitor of the renin-angiotensin system or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for the prevention of myocardial infarction (MI), stroke, cardiovascular death or overt nephropathy ~~nephropathie~~ in a diabetic patient.

Page 3, third full paragraph:

Another embodiment of the present invention is the use of an inhibitor of the renin-angiotensin system or a pharmaceutically acceptable derivative thereof together with another ~~an other~~ antihypertensive, a cholesterol lowering agent, a diuretic or aspirin in the manufacture of a medicament for the prevention of cardiovascular events, for example stroke, congestive heart failure, cardiovascular death, myocardial infarction, worsening of angina, cardiac arrest, or revascularization ~~revascularisation~~ procedures.

Page 4, second full paragraph:

A further embodiment of the present invention is a method of preventing cardiovascular events, for example myocardial infarction, worsening of angina, and cardiac arrest, comprising administering to a patient in need of such prevention an effective amount of an inhibitor of the renin-angiotensin system or a pharmaceutically acceptable derivative

thereof, particularly ~~and particular~~ in patients having an increased cardiovascular ~~cardiovascular~~ risk.

Page 4, third full paragraph:

Another ~~An other~~ embodiment of the present invention is a method of preventing myocardial infarction, stroke, cardiovascular death or overt nephropathy ~~nephropathie~~ in a diabetic patient, comprising administering to said patient an effective amount of an inhibitor of the renin-angiotensin system or a pharmaceutically acceptable derivative thereof.

Page 4, fourth full paragraph:

A further embodiment of the present invention is a method of preventing cardiovascular events, for example stroke, congestive heart failure, cardiovascular death, myocardial infarction, worsening of angina, cardiac arrest, or revascularization ~~revascularisation~~ procedures, or diabetes or diabetic complications comprising administering to a patient in need of such prevention an effective amount of an inhibitor of the renin-angiotensin system or a pharmaceutically acceptable derivative thereof together with an effective amount of another ~~an other~~ antihypertensive, a cholesterol lowering agent, a diuretic or aspirin (combination therapy).

Page 4, fifth full paragraph:

Yet another embodiment of the present invention is a method of preventing congestive heart failure in a patient not previously having congestive heart failure, comprising administering to said patient an effective amount of an inhibitor of the renin-angiotensin system or a pharmaceutically acceptable derivative thereof together with an effective amount of another ~~an other~~ antihypertensive, a cholesterol lowering agent, a diuretic or aspirin (combination therapy).

Page 5, first full paragraph:

It has been surprisingly found that cardiovascular events such as stroke, congestive heart failure, cardiovascular death, myocardial infarction, worsening of angina, cardiac arrest, or revascularization ~~revascularisation~~ procedures such as coronary artery ~~artery~~ bypass graft surgery (CABG), PTCA, Peripheral Angioplasty Surgery, Amputation, Carotid ~~Carotid~~ Endarterectomy ([])] and metabolic disorders such as diabetes ~~diabetic~~ or diabetic complications such as overt nephropathy, renal dialysis or laser therapy, or new microalbuminuria can be prevented in a broad population of high risk patients with no evidence of left ventricular ~~ventricular~~ dysfunction or heart failure, by use of an inhibitor of the RAS system.

Page 5, fourth full paragraph:

High risk patients are, for instance, those patients which are at risk of having a cardiovascular event due to a manifest coronary heart disease, a history of transient ischaemic attacks or stroke, or a history of peripheral vascular disease. Another group of high risk patients include those patients with diabetes ~~diabetic~~.

Page 5, fifth full paragraph:

The phrase "diabetes" ~~"diabetic"~~ as used herein includes both type I diabetes ~~diabetic~~, also known as insulin –dependent, diabetes ~~diabetic~~ mellitus (IDMM), and type II diabetes ~~diabetic~~, also known as non-insulin-dependent diabetes ~~diabetic~~ mellitus (NIDDM).

Page 6, second full paragraph:

Inhibitors of the RAS include ACE inhibitors, Angiotensin II antagonist and renin inhibitors and the pharmaceutically acceptable ~~accetable~~ derivatives thereof including prodrugs and metabolites.

Page 6, fourth full paragraph:

Examples Example of ACE inhibitors suitable for use herein are, for instance, the following compounds: AB-103, ancovenin, benazeprilat, BRL-36378, BW-A575C, CGS-13928C, CL242817, CV-5975, Equaten, EU-4865, EU-4867, EU-5476, foroxymithine, FPL 66564, FR-900456, Hoe-065, I5B2, indolapril, ketomethylureas, KRI-1177, KRI-1230, L681176, libenzapril, MCD, MDL-27088, MDL-27467A, moveltipril, MS-41, nicotianamine, pentopril, phenacein, pivopril, rentiapril, RG-5975, RG-6134, RG-6207, RGH0399, ROO-911, RS-10085-197, RS-2039, RS 5139, RS 86127, RU-44403, S-8308, SA-291, spiraprilat, SQ26900, SQ-28084, SQ-28370, SQ-28940, SQ-31440, Synecor, utibapril, WF-10129, Wy-44221, Wy-44655, Y-23785, Yissum, P-0154, zabicipril, Asahi Brewery AB-47, alatriopril, BMS 182657, Asahi Chemical C-111, Asahi Chemical C-112, Dainippon DU-1777, mixanpril, Prentyl, zofenoprilat, 1 (- (l-carboxy-6-(4-piperidinyl) hexyl) amino) -1-oxopropyl octahydro-1H-indole-2-carboxylic acid, Bioproject BP1.137, Chiesi CHF 1514, Fisons FPL-66564, idrapril, perindoprilat and Servier S-5590, alacepril, benazepril, captopril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, fosinoprilat, imidapril, lisinopril, perindopril, quinapril, ramipril, ramiprilat, saralasin acetate, temocapril, trandolapril, trandolaprilat, ceranapril, moexipril, quinaprilat and spirapril.

Page 7, third full paragraph:

Examples of NEP/ACE inhibitors suitable for use herein include ~~include~~ those disclosed in U.S. Patents Nos. 5,508,272, 5,362,727, 5,366,973, 5,225,401, 4,722,810, 5,223,516, 5,552,397, 4,749,688, 5,504,080, 5,612,359, 5,525,723, 5,430,145, and 5,679,671, and European Patent Applications 0481522, 0534263, 0534396, 0534492 and 0671172.

Page 9, second full paragraph:

The present invention also relates to pharmaceutical formulations comprising as active ingredient at least one RAS inhibitor and/or ~~an~~ pharmaceutically acceptable derivative thereof in addition to customary pharmaceutically innocuous excipients and auxiliaries and their use in the prevention of cardiac events and the production of medicaments therefor. The pharmaceutical preparations normally contain 0.1 to 99 percent by weight, preferably 0.5 to 95 percent by weight, of the RAS inhibitor and/or ~~[[an]]~~ a pharmaceutically acceptable derivative thereof. The pharmaceutical preparations can be prepared in a manner known per se. To this end, the RAS inhibitor and/or ~~[[an]]~~ a pharmaceutically acceptable derivative thereof are brought, together with one or more solid or liquid pharmaceutical excipients and/or auxiliaries and, if desired, in combination with other pharmaceutical active compounds, into a suitable administration form or dose form, which can then be used as a pharmaceutical in human medicine or veterinary medicine.

Page 9, third full paragraph:

Pharmaceuticals which contain a RAS inhibitor and/or ~~[[an]]~~ a pharmaceutically acceptable derivative thereof can be administered orally, parenterally, intravenously, rectally or by inhalation, the preferred administration being dependent on the particular symptoms of the disorder. The RAS inhibitors and/or ~~[[an]]~~ pharmaceutically acceptable derivatives ~~derivative~~ thereof can be used here on their own or together with pharmaceutical auxiliaries, namely both in veterinary and in human medicine.

Page 11, second full paragraph:

The RAS inhibitors and/or ~~[[an]]~~ pharmaceutically acceptable derivatives ~~derivative~~ thereof can also be used to achieve an advantageous therapeutic ~~therapeutic~~ action together with other pharmacologically active compounds for the prevention of the abovementioned syndromes.

Page 11, fourth full paragraph:

The invention additionally relates very generally to the combination of a RAS inhibitor and/or ~~[[an]]~~ a pharmaceutically acceptable derivative thereof with a cholesterol ~~cholesterol~~ lowering agent.

Page 11, fifth full paragraph:

In addition to administration as a fixed combination, the invention also relates to the simultaneous, separate or sequential administration of an RAS inhibitor and/or ~~[[an]]~~ pharmaceutically acceptable derivative thereof with another ~~an other~~ antihypertensive, a cholesterol lowering agent, a diuretic or aspirin.

Page 11, sixth full paragraph:

The invention additionally relates to a pharmaceutical preparation comprising an RAS inhibitor and/or ~~[[an]]~~ a pharmaceutically acceptable derivative thereof and a cholesterol lowering agent (combination product).

Page 12, first full paragraph:

The weight ratio of the RAS inhibitor and/or ~~[[an]]~~ a pharmaceutically acceptable derivative thereof and the cholesterol lowering agent in the novel combinations and preparations lies in the range from 1:0.01 to 1:100, preferably 1:0.1 to 1:10.

Page 13, first full paragraph:

"Combination therapy" will also include simultaneous or sequential administration by intravenous, intramuscular or other parenteral routes into the body, including direct absorption through mucous ~~mucous~~ membrane tissues, as found in the sinus passages. Sequential administration also includes drug combination where the individual elements may be administered at different times and/or by different routes but which act in combination to provide a beneficial effect.